Lipid Synthesis

Introduction

Fatty acid synthesis, the subject of this lesson, occurs in the **insulin-dominant hepatocyte**. In the insulin-dominant state, cells are taking up glucose, burning it to make ATP, and storing it as glycogen. They're using and storing. In the carbohydrate metabolism section, we learned that this means "glycolysis"; in glycogen metabolism, we learned that it means "glycogen storage"; and now we'll learn, in the fatty acid section, that it means "fatty acid synthesis."

In Metabolism #9: *Carbohydrate Regulation*, we mentioned that an insulin-dominant hepatocyte would do more than simply choose between glycolysis and gluconeogenesis, that the substrate-level regulation would help the hepatocyte prioritize reactions. The first reaction that must occur in the insulin-dominant state is glycolysis, the default of all cells. But when cells become rich in ATP, substrate-level regulation turns off the steps of glycolysis—inhibiting pyruvate dehydrogenase and inhibiting isocitrate dehydrogenase of the Krebs cycle. Even in skeletal muscle, reduced glycolysis with extra glucose shifts the insulin-dominant skeletal muscle cell to build glycogen. Glycogen is built only after ATP stores are flush.

So too in the hepatocyte. As ATP levels rise, NADH levels rise, acetyl-CoA becomes abundant, and the PDH-TCA-ETC pathway is inhibited. **Extra glucose is instead pushed into glycogen storage** (Metabolism #11: *Glycogen Metabolism*). But the pancreas knows the liver better than that. With **insulin**, and this is true only in the hepatocyte, pyruvate dehydrogenase is dephosphorylated and activated, ensuring that more acetyl-CoA is made despite substrate-level regulation inhibiting PDH. And even though the hepatocyte is flush with ATP, insulin dominance remains, and so gluconeogenesis is off. So what does the liver do with **excess pyruvate, acetyl-CoA, and a bunch of high-energy molecules** (ATP, NADH)?

That is fatty acid synthesis. We'll discuss fatty acid nomenclature, activation, and synthesis in the hepatocyte in this lesson, discuss transport to and from adipose and how adipose stores fatty acids (in Metabolism #14: *Triglyceride Mobilization*), then discuss how fatty acids are mobilized and consumed (in Metabolism #15: *Lipid Catabolism*). This process does involve learning about cholesterol as well, but we save the synthesis and pharmacology for cardiology.

Fatty Acid Nomenclature

Fatty acids are long strings of carbon, with the **carboxylic acid** (the COOH) at the **1 position**. We designate the carbon at **position 2 as "α" (alpha)**. How we write fatty acids is unfamiliar to most medical students but is also quite informative. Strings of carbons linked together have either a single bond or a double bond. We name a fatty acid by how many **carbons total**, then a colon, then the **number of double bonds**. The parentheses that follow give the exact position of the double bonds.

C16:0 is a 16-carbon-long chain, with no double bonds. The absence of double bonds is referred to as **saturated**. Any double bonds, and the chain is **unsaturated**. The fatty acid our body makes, **palmitic acid**, is saturated. Our body makes only saturated fats. It can metabolize more than that, but the body likes saturated fats.

C18:2 (9,12) is an 18-carbon-long chain, with two double bonds, found at positions 9 and 12. Therefore, it's unsaturated. This is **linoleic acid**.

C18:3 (9,12,15) is an 18-carbon-long chain, with three double bonds, found at positions 9, 12, and 15. Therefore, it's unsaturated. This is **linolenic acid**.

Only **unsaturated fats**, such as the omega family, have additional properties and a *trans*- or *cis*-conformation. The **omega family** of a fatty acid is determined by the **chain length minus the last double-bond position**. The bird's-eye view is in relation to heart disease. Because arachidonic acid is a precursor to prostaglandins, thromboxanes, etc., and **fatty acids make up the lipid bilayer of our cells**, if we have too much arachidonic-acid-like fat (too much omega-6 instead of omega-3), we may increase our risk of heart disease. Double bonds in fatty acids made by organisms are in **cis-conformation** and **increase membrane fluidity**; they're necessary to make the lipid bilayer. **Trans-conformation** fatty acids are **synthetic** and worsen membrane fluidity. Both unsaturated, and worse, trans-unsaturated fats are unhealthy, whereas saturated fats are quite essential. Omega-3's are good. Omega-6's are bad.

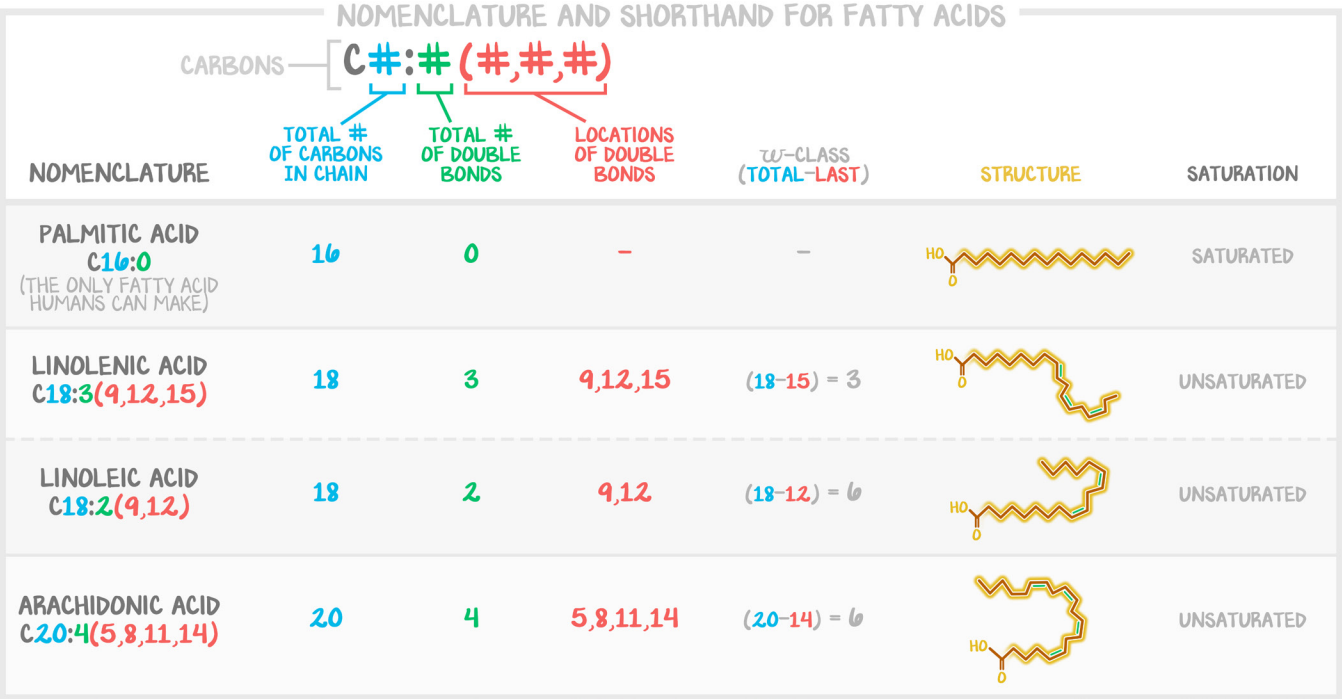

Figure 13.1: Nomenclature and Shorthand for Fatty Acids
Link each column before the structure (and their color) with the shorthand represented in the Name column to piece together the meaning of the numbers in the shorthand name.

FATTY ACID	HEADERS MISSING	TOTAL - FINAL	OMEGA CLASS
Linoleic Acid	C18:2 (9,12)	18-15 = 6	Omega-6
Linolenic Acid	C18:3 (9,12,15)	18-15 = 3	Omega-3
Arachidonic Acid	C20:4 (5,8,11,14)	20-14 = 6	Omega-6

Table 13.1: Omega Families
Despite completely different structures and completely different shorthand appearance, the omega class makes seemingly unrelated fatty acids function similarly. Conversely, fatty acids with near-identical names but in different omega classes function completely differently.

Fatty Acid Activation

To do anything with a fatty acid, it must first be **activated** with ATP and CoA. Fatty acids are built when energy is abundant: excess nutrients now can be used later. When **building fatty acids**, any carbon structure needs to be **energized**, referred to as activated, with **CoA**. Acetate (2 carbon) + CoA is acetyl-CoA. Palmitate (16 carbon) + CoA is palmitoyl-CoA. The CoA just means "I'm carrying energy."

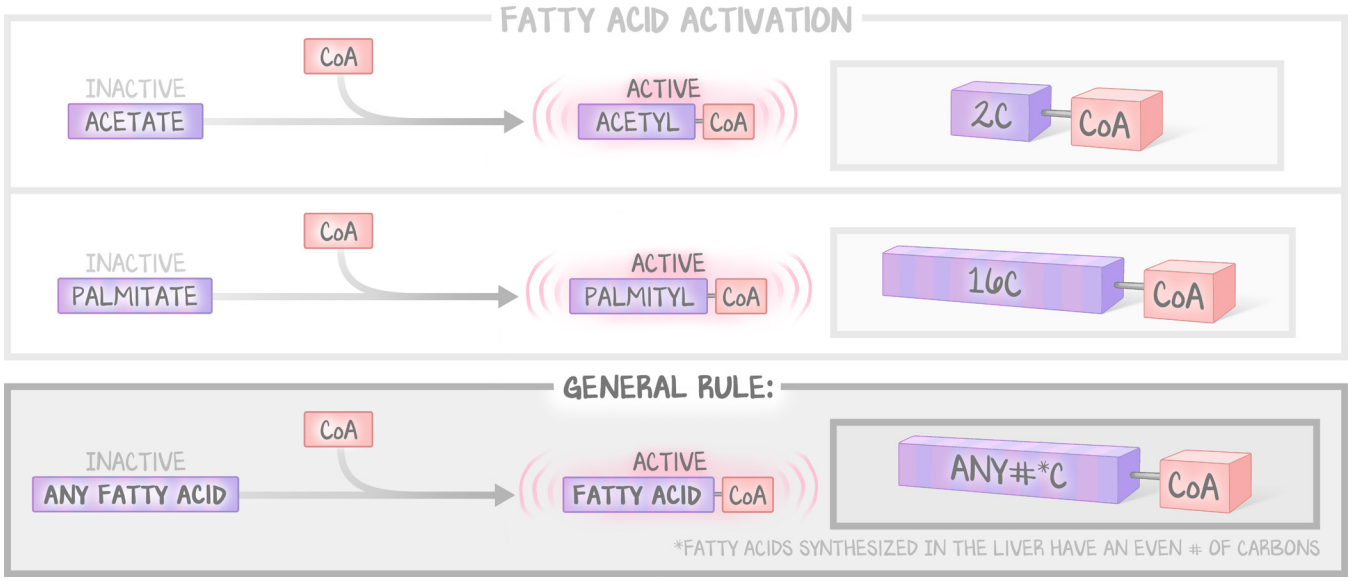

Figure 13.2: Fatty Acid Activation
The addition of a CoA to any fatty acid "activates" that fatty acid.

Fatty Acid Synthesis

This is occurring in the insulin-dominant state, so insulin will increase fatty acid synthesis. The substrate needed is **acetyl-CoA** and **CO_2** (notice that the substrate is NOT glucose). The enzymes are **acetyl-CoA carboxylase** and **fatty acid synthase**. Acetyl-CoA carboxylase takes acetyl-CoA and makes malonyl-CoA. Fatty acid synthase adds a total of eight acetyl-CoA to form the C16:0 fatty acid palmitate.

In fatty acid synthesis, both the location and hormones involved matter. It's made possible because the liver is in the **insulin-dominant state** and is flush with energy. In the insulin-dominant state, glycolysis is favored, with an extra push of pyruvate dehydrogenase from insulin. This ensures that glucose is turned into acetyl-CoA. Excess glucose is turned into glycogen in the cytoplasm. Then, if there's still excess glucose, it will be turned into fatty acids in the cytoplasm. The glucose is turned first into acetyl-CoA in the mitochondria, then that acetyl-CoA gets to the cytoplasm to finish the assembly.

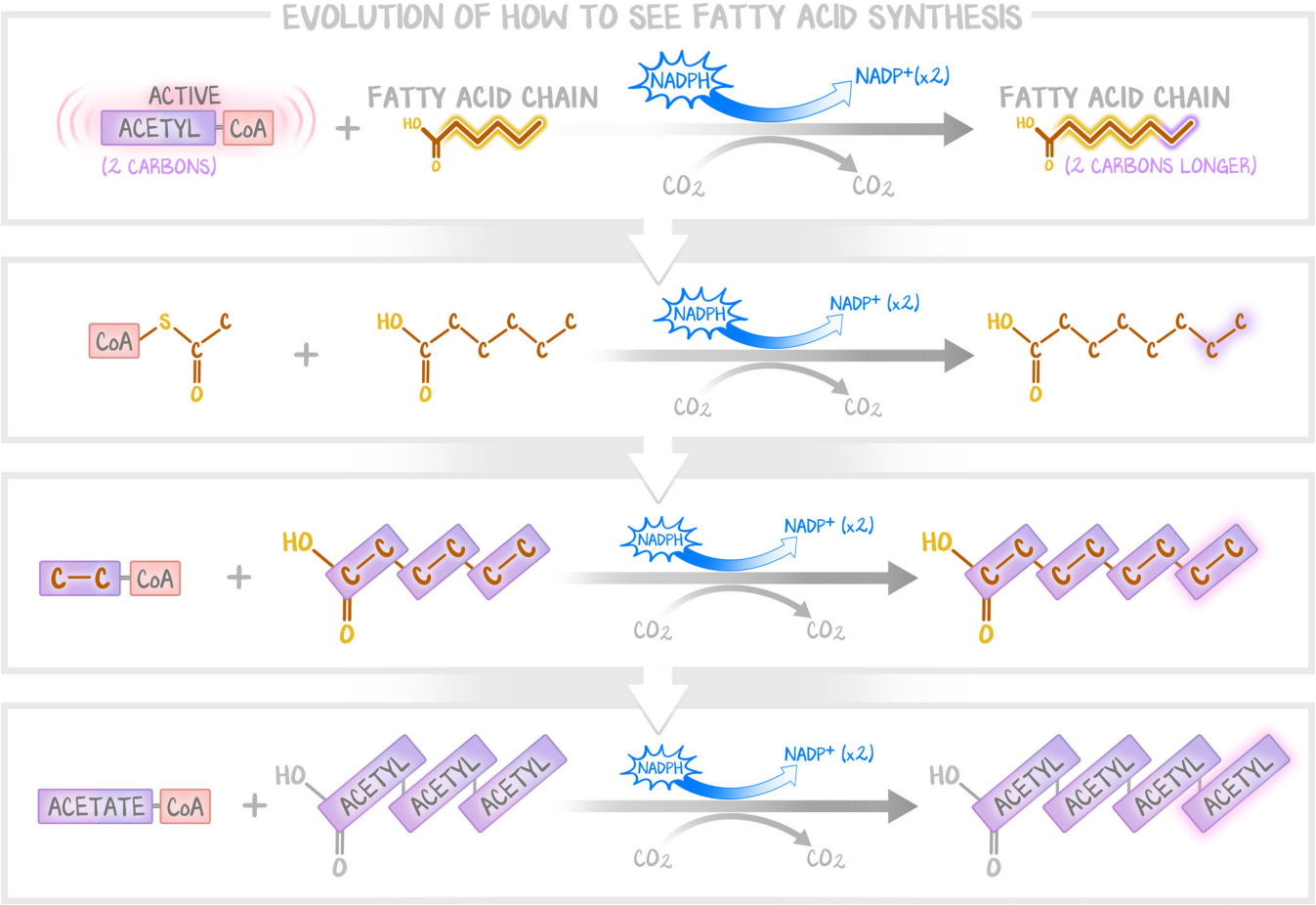

Figure 13.3: Net Reaction of Fatty Acid Synthesis and the Evolution Of Fatty Acid Visualization
At the cost of two NADPH, an acetyl-CoA (2 carbons) is incorporated to elongate the growing fatty acid chain. The two-carbon acetate molecule can be charged with CoA to form acetyl-CoA, its charged form that can be added to the growing carbon chain. The CoA is released in order to create the bond between the two new carbons and the existing chain, the two carbons added in the last reaction. In a sense, each carbon is not a singular unit; rather, the two-carbon acetate is the unit of storage that can be charged to acetyl-CoA, capable of entering the citric acid cycle. Palmitate, the 16-carbon fatty acid, should instead be seen as an "8-acetate fatty acid," formed by the addition of eight acetyl-CoA.

Acetyl-CoA comes from glucose catabolism through the formation of pyruvate in the cytoplasm and acetyl-CoA in the mitochondria. This acetyl-CoA should be used for TCA-ETC to make energy. When energy is abundant, the TCA slows down. That acetyl-CoA is then in excess and can be used for fatty acid synthesis. Pyruvate, in the same pathway as gluconeogenesis, uses **pyruvate carboxylase** to become oxaloacetate. Using the **citrate shuttle**, oxaloacetate and acetyl-CoA make citrate and **leave the mitochondria**. We said (in Metabolism #5: *Citric Acid Cycle*) that the acetyl-CoA enters the cycle, spins the wheel 360°, and that's it. But now we reveal more truth. Because the NADH, ATP, and acetyl-CoA levels are high, isocitrate dehydrogenase (the rate-limiting step of the Krebs cycle) and pyruvate dehydrogenase (pyruvate to acetyl-CoA) are inhibited while pyruvate carboxylase is disinhibited. That also means that the citrate that gets formed in this state **has nowhere to go**. It too would accumulate, except that the **citrate shuttle** removes it from the mitochondria. The citrate in the cytoplasm releases the oxaloacetate and heads back to pyruvate, while that **acetyl-CoA** goes on for **cytoplasmic fatty acid synthesis**.

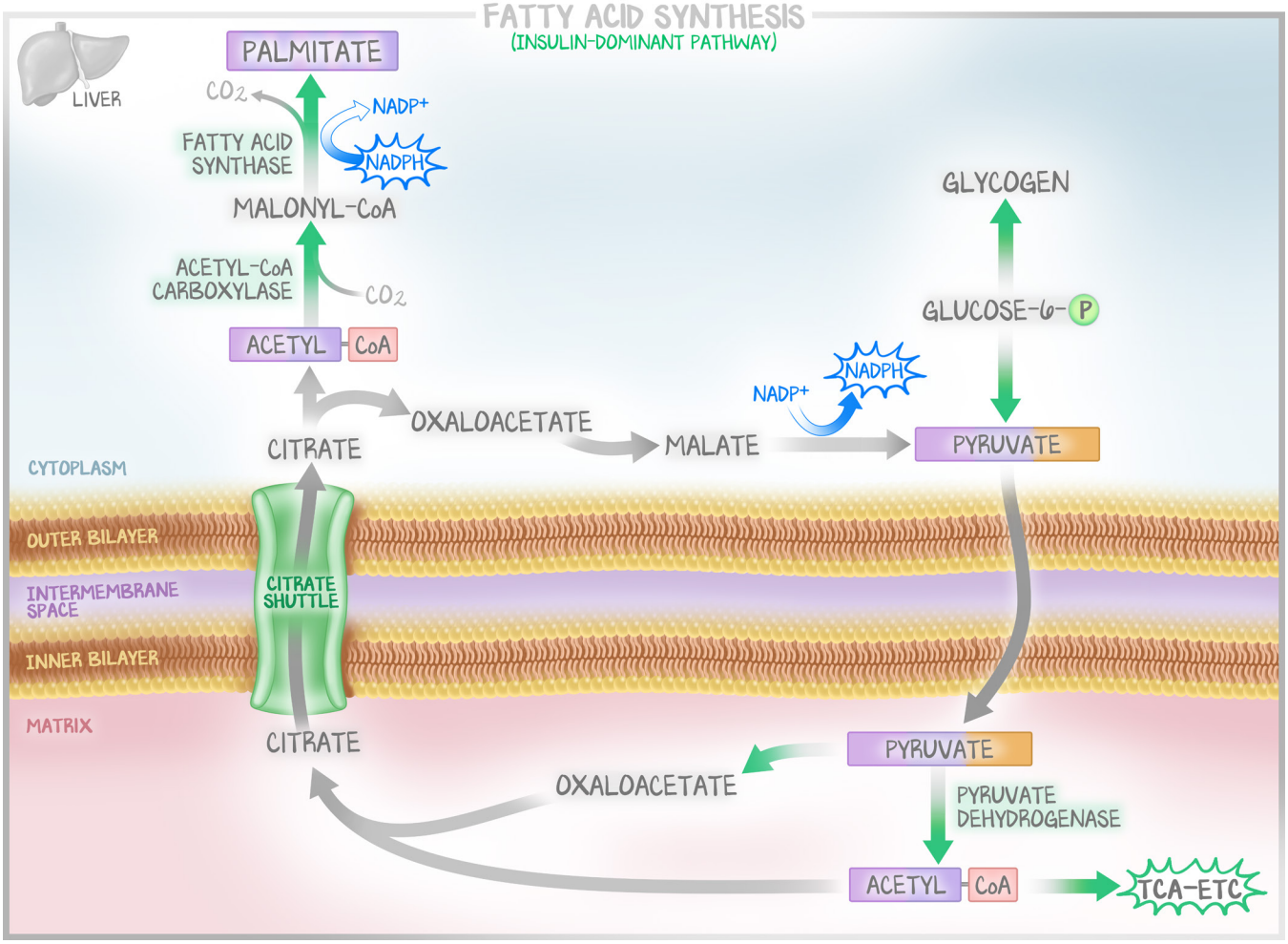

Figure 13.4: How Insulin Affects Fatty Acid Synthesis
Insulin pushes glucose to glycogen and glucose to acetyl-CoA. That acetyl-CoA is used for energy in TCA-ETC. Once there is enough ATP, the excess acetyl CoA created by glycolysis is funneled through the citrate shuttle, where that same acetyl-CoA can be incorporated into a growing chain of acetates, called fatty acids.

These statements are relevant because, if you look at a summary slide of metabolism, you might be tricked. Pyruvate goes to oxaloacetate under the influence of glucagon to enter gluconeogenesis through the malate shuttle. Pyruvate goes to oxaloacetate under the influence of insulin to enter fatty acid synthesis through the citrate shuttle. Acetyl-CoA is used, under insulin, for **lipid synthesis in the cytoplasm**. That acetyl-CoA comes from glycolysis and pyruvate dehydrogenase.

Citrate is a major **substrate-level regulator**. It **activates** acetyl-CoA carboxylase in a **feed-forward** mechanism. Acetyl-CoA carboxylase is the rate-limiting step. Citrate also inhibits PFK-1.

In the **insulin-dominant state**, it'd make sense to hear that **insulin stimulates acetyl-CoA carboxylase** (by dephosphorylating) and that **insulin induces fatty acid synthase** (increases gene expression). So, while the hepatocyte flips toward the insulin world, it burns glucose and generates ATP. All the while, gene expression has shifted toward making more pyruvate (glucokinase induction from carbohydrate metabolism) and fatty acids (fatty acid synthase). By the time gene expression has increased the number of proteins for fatty acid synthesis (by the time fatty acid synthase has been fully induced), glycolysis has made acetyl-CoA, ATP, and NADH abundant, so that not only is there more fatty acid synthase around, the cell's state is also flush with high-energy molecules, creating an environment that favors fatty acid synthesis.

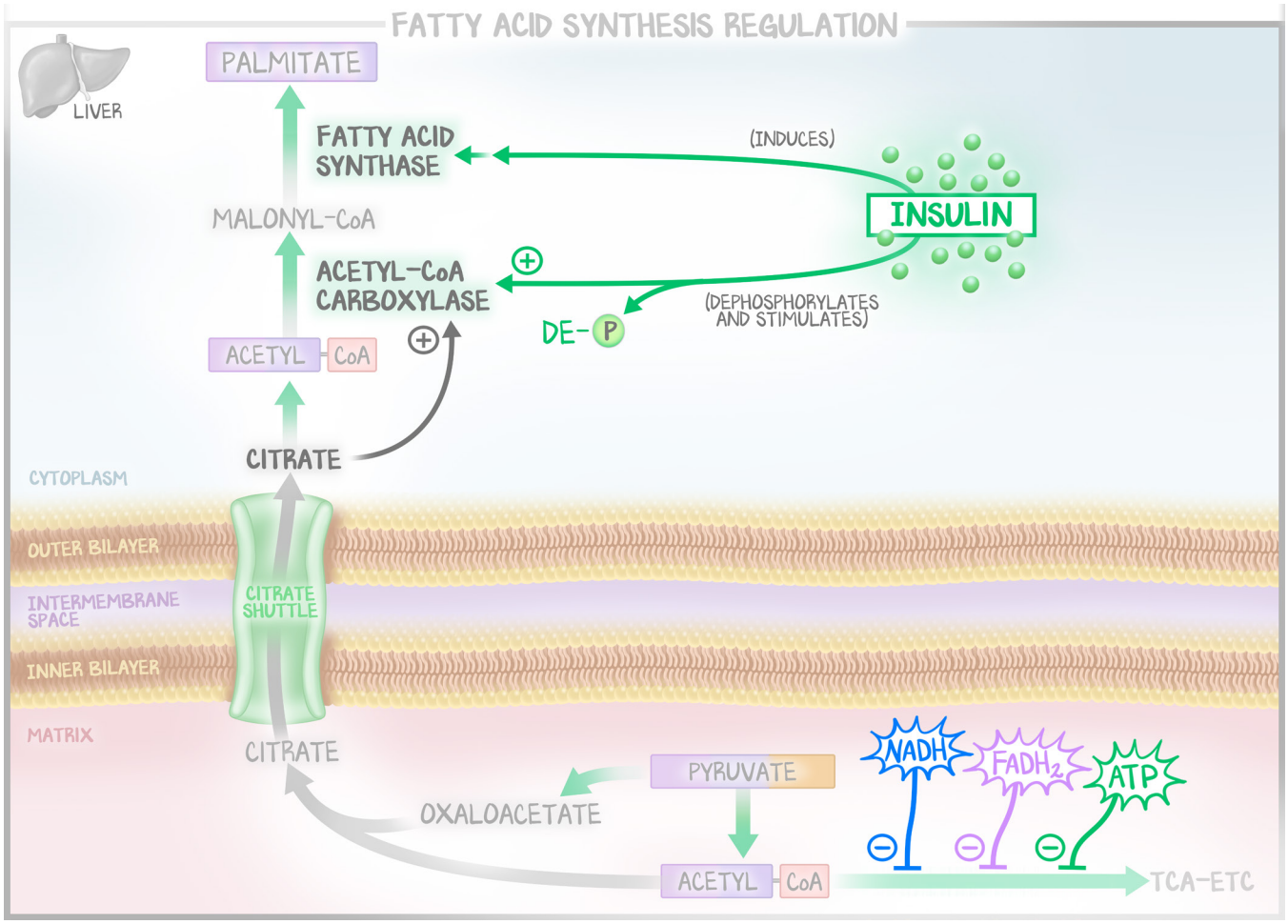

Figure 13.5: Fatty Acid Synthesis Regulation
Fatty acid synthesis occurs only when there is insulin stimulation and there is sufficient energy. This allows the acetyl-CoA that would be used for TCA-ETC to instead be used to store the energy as lipid.

Acetyl-CoA carboxylase requires **ATP**. It takes acetyl-CoA, **adds a carboxyl group** (COO^-) and makes **malonyl-CoA** (Figure 13.6). Two things should be apparent. One, malonyl is still "activated" because it has CoA. Two, acetyl-CoA had two carbons, now malonyl has three carbons, and one of those carbons is a carboxyl group. Malonyl-CoA could be written as C3:0; a 3-carbon sugar with a carboxyl group in the 1 position, and no double bonds.

Fatty acid synthase continues to add carbons together, one acetyl-CoA at a time. **Palmitate**, palmitic acid, C16:0, is the **only fatty acid a human can make**. How, then, is malonyl-CoA, a 3-carbon sugar, able to make a chain 16 carbons long? Fatty acid synthase's net effect is to take "whatever-the-chain-is" and add two carbons; the **fatty acid chain is made of only acetyl-CoA**. It takes an even number of carbons (the chain) and adds to it an acetyl-coA, which is also an even number of carbons. The trick here is that CO_2 is used by acetyl-CoA carboxylase to activate the acetyl-CoA. Malonyl-CoA is released when acetyl-CoA is attached to the growing fatty acid. The 3-carbon structure is merely an intermediate; that third carbon isn't incorporated into the growing fatty acid chain. (Figure 13.7)

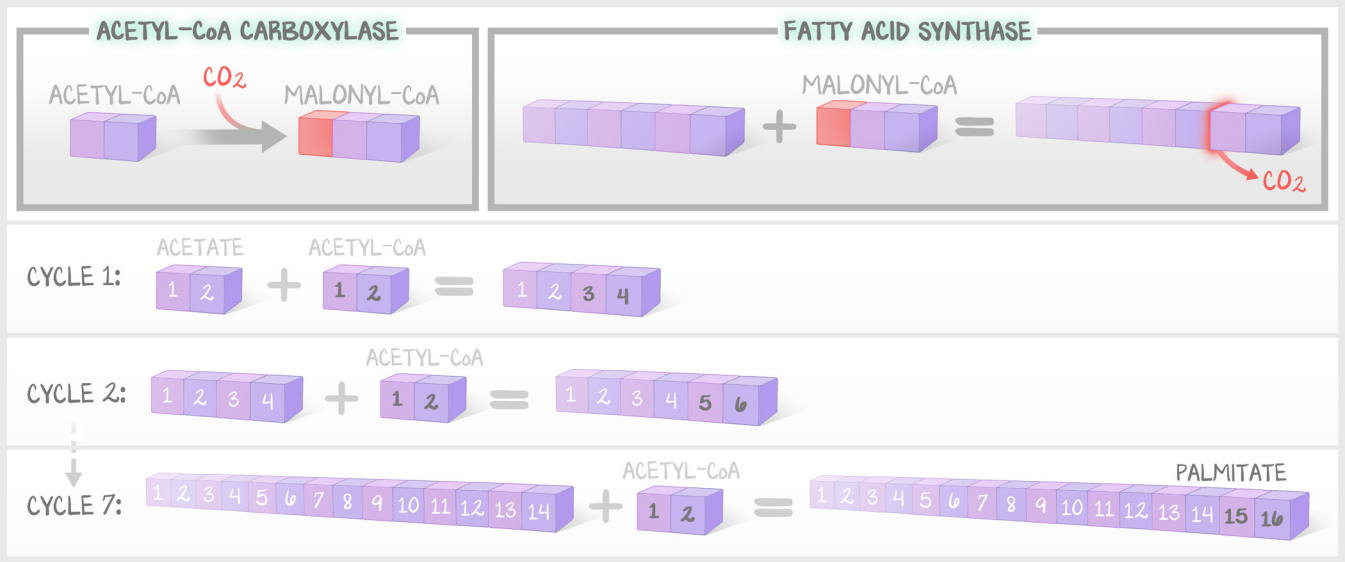

Figure 13.6: Fatty Acid Synthase
The first step is to add a carbon to acetyl-CoA, forming malonyl-CoA. That carbon is released when malonyl-CoA is attached to the growing fatty acid chain, resulting in a net increase of two carbons.

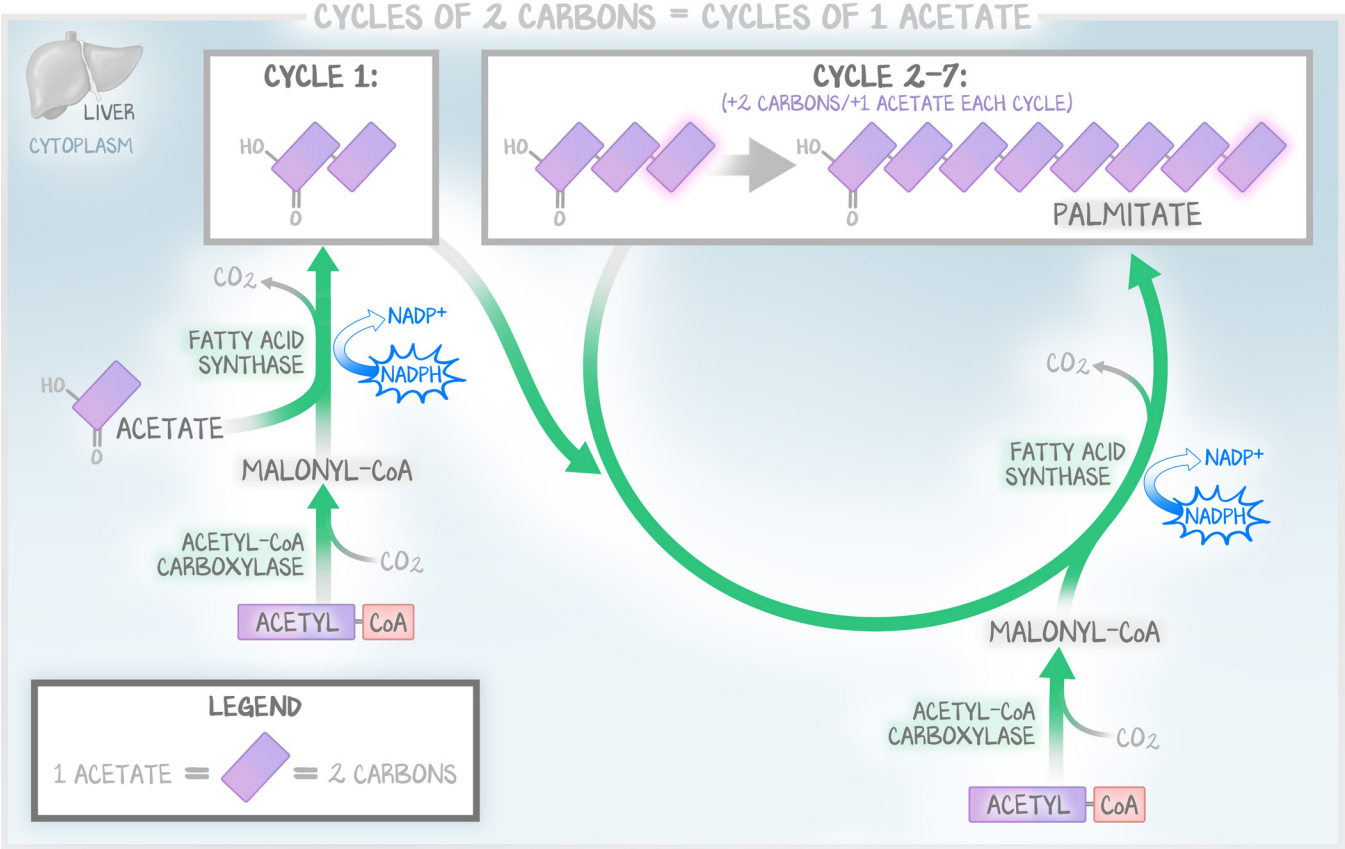

Figure 13.7: Fatty Acid Synthesis Stores Acetates as Fatty Acids
Each palmitate has a 16-carbon chain, which can be visualized as a chain of eight 2-carbon units. Excess acetyl-CoA (2 carbons) is shunted to the cytoplasm, where it is converted to malonyl-CoA and added to a 2-carbon acetate by fatty acid synthase, forming a 4-carbon or 2-acetate carbon chain (Cycle 1). With each additional cycle, acetyl-CoA is converted to malonyl-CoA and added to the growing chain, extending it from 4 carbons/2 acetates to 6 carbons/3 acetates, etc. Each cycle, another acetate is added to the fatty acid chain. Therefore, acetate is the basic unit that spins the citric acid cycle, and the energy is not stored in the bonds between individual carbon molecules but rather the bonds between acetates.

Beyond this, the intermediate steps of fatty acyl-CoA that allow for elongation, desaturation, and other details aren't needed. Skip them.

NADPH Is Required for Fatty Acid Synthase

This is a massively simplified version of what you need to know. Glycolysis makes NADH in the cytoplasm. It takes an NAD, and the dehydrogenase steps in the cytoplasm make NADH. If an $NADP^+$,were present, it could be used like NAD, and the dehydrogenase used to make NADPH. So although we taught that NAD → NADH (in Metabolism #3: *Glycolysis*), it can also be understood as NADP → NADPH. The only difference is that the NADH goes to the electron transport chain for ATP and NADPH is used for fatty acid synthase. For every **one cycle of fatty acid synthase**, there are **two NADPH used**. To make palmitate, 16 carbons long, or eight acetyl-CoA long, will have to have seven cycles—the starting two carbons from the first acetyl-CoA, and then seven added acetyl-CoA. This means (and because it's NOT 2 × 8 = 16, it's a board favorite) that **14 NADPH** are used for **seven cycles of fatty acid synthase** to make a **16-carbon-long fatty acid**.